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Risk factors for histologically confirmed benign breast tumors

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Abstract. A case-control study of 156 cases of various types of benign breast disease (BBD) and 156 population controls was conducted to investigate the role of various behavioral, reproductive, and hormonal factors in the etiology of these breast disorders. Our results indicate that the distinct histological groups of BBD differ from each other in respect to possible risk factors. Small sample size poses severe restrictions on the conclusiveness of the results and thus they should be considered as preliminary and suggestive. Our results do not support the notion that BBD could be considered as a uniform entity with common risk factors.

Key words: Benign, Breast, Epidemiology, Risk, Tumor

Abbreviations: BBD = benign breast disease; BC = breast cancer; OR = oral contraceptive

Introduction

The studies of benign breast disease (BBD) can be divided into two categories: those interested in BBD as a possible intermediate end-point of breast cancer [1–4] and those focusing on BBD as a possible result of a specific causal factor, such as oral contraceptives [5, 6]. In the second category, the underlying concern is often also the possible link between BBD and breast cancer (BC).

The studies in the first category look for common risk factors, estimate the risk of breast cancer attributable to BBD, and investigate the role of BBD in the pathogenesis of BC. The main goal is to be able to identify a precursor state and thus prevent the development of the much more perilous end-point.

The numerous and diverse attempts to establish a definitive link between BBD and BC have not been able to produce consistent and conclusive results. Largely this is due to the absence of common clinical and histological classifications, pooling of a number of distinctly different histological entities, or absence of suitable control populations. Unfortunately, routine histological reporting is to a considerable degree subjective. In addition, the lack of a uniform histological classification system and nomenclature greatly enhances the confusion and reduces the possibilities for comparing different studies [7].

The present study was aimed at investigating risk factors for several distinct histological subgroups of benign breast disease.

Subjects and data collection

Cases. The eligibility criteria of the cases were: (1) age 35 to 69 years, (2) residency in the Helsinki metropolitan area, (3) breast lump with no indication of malignant process or metastasis, and (4) no previous cancer of any organ.

The seven largest referral clinics participated in the recruitment of cases. Patients attending because of a breast lump and meeting the eligibility criteria were asked to participate. In most cases (75%) recruitment took place before the diagnostic procedures and thus without the woman knowing the histology of the lump. Those consenting to participate were given the background questionnaire at the initial contact, for completion at home. Participants were studied as soon as possible after the initial contact. In most cases the interval was 1–2 days, and in all cases less than one week. In all, 223 breast lump cases were interviewed during a period of 28 months. Sixty-seven of these had a malignant tumor and 156 a benign tumor, as diagnosed subsequently. The results concerning the malignant tumors have been reported elsewhere [8] and this report includes only the benign cases.

The response rate for the benign tumors is impossible to calculate accurately due to the lack of a national registry. All cases were histologically classified by the diagnosing clinic using the ICD-9. Among the 156 benign tumors there were 56 cases of mastopathia chronica cystica (MCC; ICD 6101), 25 cases of fibroadenomatosis (FAM; ICD 6102), 26 cases of cysts (ICD 6100), and 49 other benign tumors. The latter group consisted of 21 benign dysplasias (ICD 6108 and 6109) and 28 unspecified benign neoplasms of breast (ICD 217).

Controls. Community controls were selected randomly from women in the National Population Register. The same age and residency requirements were used as for the cases. In a letter that described the aims and procedures of the study and asked the recipient to make an interview appointment, controls were invited to participate. The invitation letter was accompanied by the background information questionnaire. If no reply was received within two weeks of mailing the invitation, a second letter was sent. No further attempts were made to contact the women.

The recruitment of controls was syncronized as much as possible to the accrual of cases. Invitation letters were sent to 321 women. A total of 164 (51%) women attended the interview, while 57 (18%) declared reluctance or practical difficulties, and 100 (31%) made no reply. Using the same exclusion criteria as with the cases, eight women were omitted from the final analysis because they had had cancer of the breast, uterus, or colon. Thus 156 women constituted the control group.

Data collection. Cases and controls were interviewed by one of the three study nurses. During the interview visit, the nurse checked the questionnaire completed by the subject at home, and made any necessary amendments. The questionnaire concerned demographic factors (type of residential area, education, occupation, marital status), as well as general medical, gynecological, family, and smoking histories. During the visit the nurse measured the weight and height of the participant. Childhood and adolescent weight and height were estimated by the participants themselves with five-level scales.

Age at menarche was taken as the year when the menses first appeared. No attempt was made to gather details on the regularity or type of menses at their onset. Age at menopause was taken as the year the participant reported cessation of menstruation. Breast size was recorded as the cup size of bra usually worn by the woman. The four reported cup sizes were reduced to two breast sizes for analysis: small (A and B) and large (C and D).

Statistical analyses. Logistic regression models [9] were used to assess the effects of risk factors on the log odds of disease. First, linear trends of continuous variables were tested. For further analyses certain variables were dichotomized or divided into tertiles using cutting points determined on the basis of the combined group of cases and controls. Odds ratios (OR) were calculated using the lower group or lowest tertile as reference group and confidence intervals were calculated as the antilog of the [$\ln OR \pm 1.96(SE_{\ln OR})$]. Age was considered an important confounding variable and all relevant odds ratios were adjusted for age (treated as a continuous variable). When studying variables that were not relevant for all women, such as age at first birth or years smoked regularly, the analyses were confined to those women who had experienced the event or exposure.

Results

The characteristics of the cases and controls are presented in Table 1. In addition to the factors presented in the table, residency distribution and social and occupational classification were also studied and no differences between the cases and controls were found.

Age was inversely related to risk of disease in all of the four histological groups (Table 2). This effect was most pronounced and consistent in the FAM group. Age at menarche and menopausal status were not related to risk of having a benign breast tumor. Age at menopause was similarly unrelated (not shown). There was a clear difference between the different types of benign tumors in the effect of (late) age at first childbirth. It increased the risk of FAM four-fold, but did not enhance the risk of other types. A somewhat similar, though opposite pattern was seen with the effect of parity. Parous women had a statistically significantly lower risk of FAM and cysts when compared to the nulliparous. Among parous women, the number of children did not affect risk (not shown).

Factors characterizing certain aspects of the menstrual cycle, namely the length and regularity of menstrual cycles, and menstrual breast tenderness, were not statistically significantly related to changes of the risk of benign breast tumors (Table 2).

Mastitis occurring in a non-lactating breast increased the risk of cysts six times greater than never having any kind of mastitis (OR 6.1, 95% CI 1.1, 33.5). The other types of benign tumors were unrelated to this factor. Relative risk of MCC, FAM, and cysts was not affected by puerperal mastitis.

The relationship between certain anthropometric measures and the risk of benign breast tumors is presented in Table 3. Body size characterized by body mass index (BMI; weight (kg)/height^2 (m)) and breast size were inversely related to the risk of FAM, but not the other subgroups of benign breast tumors. However, the effect of breast size was not independent of BMI and adjusting for BMI made the odds ratio for FAM statistically insignificant. Height alone was not associated with risk in any of the tumor subgroups. We also analyzed the possible role of childhood and adolescent weight and height as predictors of later risk of benign breast tumors. Neither BMI nor height during either developmental period was correlated to later risk.

Table 1. Characteristics of the study population. Participants were recruited from the metropolitan area of Helsinki, Finland in 1984–85. Cases were diagnosed as having a benign breast tumor and controls were random community controls

Factor	Cases (n = 156)		Controls (n = 156)	
	Mean or %	(SEM)	Mean or %	(SEM)
Age (years)	54.7	(1.0)	51.3	(1.1)
Age at menarche (years)	13.7	(1.4)	13.5	(1.5)
Length of menstrual cycles (days)	26.4	(0.5)	26.5	(0.2)
Parous (%)	65.7		77.7	
Parity (childbirths)	1.4	(0.2)	1.6	(0.1)
Age at first birth (years)	25.5	(0.6)	25.4	(0.4)
Total lactation time (months)[a]	8.27	(1.6)	7.91	(0.9)
Menstrual breast tenderness (%)	80.3		70.7	
Age at menopause (years)	50.3	(0.5)	49.4	(0.5)
Postmenopausal (%)	61.2		42.0	
OC users (%)	25.4		29.3	
Use of OC (years)	5.4	(0.9)	4.5	(0.5)
Non-OC estrogen users (%)[b]	43.3		28.7	
Use of estrogen (years)	7.2	(1.2)	3.7	(0.6)
Bra cup size (%)				
small	67.3		54.5	
large	32.7		45.5	
Smoking status (%)				
never	53.2		67.3	
ex-smoker	19.2		12.8	
current	27.6		19.9	
Years smoked regularly[c]	20.9	(1.8)	16.5	(1.3)
Number of cigarettes per day[c]	14.1	(2.0)	13.6	(1.0)

OC = oral contraceptive; SEM = standard error of the mean.
[a] Everlactated only.
[b] Non-OC = estrogen replacement therapy.
[c] Ever smokers only.

Oral contraceptive (OC) use increased the risk of MCC, but was not related to the risk of other types of benign tumors (Table 4). The results suggest a time-dependent effect with a two-fold increase after OC use for less than five years and a three-fold increase after OC use for five years or more. Use of estrogen supplementation did not affect the risk of benign tumors.

Discussion

The recruitment of cases took place in the largest referral clinics in the city of Helsinki. This was due to practical limitations of the study organization. Since many of the breast lumps that appear clinically benign are biopsied and histologically verified through numerous local public or private outpatient clinics, it is very difficult to estimate the yield of our accrual method. It is possible, and even probable, that the cases are not a representative sample of women with breast lumps in general, but rather of those whose lump is clinically suspicious.

The primary and leading reason for recruiting women with a breast lump was to investigate risk factors for malignant breast tumors [8]. The accumulation of cases with a malignant tumor was thus the impetus for the whole process. The number of different benign breast tumors was not preplanned and no formal power calculations were performed. Small sample size poses severe restrictions on the conclusiveness of the results and thus they should be considered at most as preliminary and suggestive. The fact that the number of controls is exactly the same as that of the cases is an unintended coincidence. No 1:1 matching was attempted, but statistical methods were used to control for possible confounding variables.

The apparent protective effect of age is understandable considering the age structure of the study population. The peak incidence age of BBD is around 40 years, MCC between 40 to 50 years, and that of FAM between 25 to 30 years [10–14]. These are diseases of physiologically active breast tissue, and with the involution of the glandular tissue their incidence decreases [15].

The milestones and various characteristics of the reproductive life of a woman do not form as convincing a risk profile for BBD as in the case of malignant breast tumors [14, 16]. Age at menarche has in

Table 2. Age, hormonal and reproductive factors, and the relative risk of benign breast tumors. The number of subjects in each histologic category indicate the total number of cases in that group

Factor	Benign tumor group			
	MCC (n = 56)	FAM (n = 25)	Cyst (n = 26)	Other (n = 49)
Age				
≤ 44	1.0[a]	1.0	1.0	1.0
45–54	0.6 (0.3, 1.1)[b]	0.3 (0.1, 0.7)	0.9 (0.4, 2.4)	1.0 (0.4, 2.1)
≥ 55	0.2 (0.1, 0.6)	0.1 (0.0, 0.4)	0.4 (0.1, 1.2)	0.6 (0.3, 1.5)
Age at menarche ≤ 13 years vs. more	0.9 (0.5, 1.8)	1.9 (0.7, 5.8)	1.4 (0.5, 3.7)	1.2 (0.6, 2.6)
Age at first birth[d] ≥ 28 years vs. less	0.7 (0.3, 1.6)	4.5 (1.3, 15.3)	0.9 (0.3, 2.7)	0.6 (0.3, 1.3)
Parity parous vs. nulliparous	0.7 (0.3, 1.5)	0.2 (0.1, 0.7)	0.4 (0.1, 0.9)	0.9 (0.4, 1.9)
Total lactation time[d] ≥ 6 months vs. less	0.9 (0.4, 1.7)	0.9 (0.3, 2.2)	0.6 (0.2, 1.7)	1.2 (0.6, 2.3)
Length of menstrual cycle ≥ 25 days vs. less	0.7 (0.3, 1.4)	0.2 (0.0, 1.6)	0.6 (0.2, 1.4)	0.9 (0.4, 2.0)
Menstrual cycles regular vs. irregular	1.1 (0.4, 3.0)	NC[c]	1.3 (0.3, 4.8)	1.1 (0.4, 3.2)
Menstrual breast tenderness yes vs. no	2.1 (0.9, 5.2)	1.0 (0.3, 2.9)	2.5 (0.7, 8.9)	1.5 (0.7, 3.4)
Menopause post- vs. premenopausal	1.0 (0.3, 2.7)	1.4 (0.3, 8.0)	0.4 (0.1, 2.3)	1.4 (0.5, 4.1)

MCC = mastopathia chronica cystica; FAM = fibroadenomatosis.
[a] Odds ratio; all other factors adjusted for age, except for age itself. [b] 95% confidence interval. [c] No cases in one of the groups. [d] Parous only.

Table 3. Body mass index, height, breast size, and the relative risk of benign breast tumors

Factor	Benign tumor group			
	MCC (n = 56)	FAM (n = 25)	Cyst (n = 26)	Other (n = 49)
Body mass index ≥ 26 vs. less	0.7[a] (0.3, 1.3)[b]	0.3 (0.1, 0.9)	0.9 (0.4, 2.2)	0.9 (0.5, 1.8)
Height ≥ 162 cm vs. less	0.9 (0.4, 1.7)	0.9 (0.3, 2.5)	1.3 (0.5, 3.2)	0.6 (0.3, 1.2)
Bra cups large vs. small	0.8 (0.4, 1.5)	0.2 (0.1, 0.7)	0.6 (0.3, 1.5)	0.9 (0.4, 1.7)

MCC = Mastopathia chronica cystica; FAM = fibroadenomatosis.
[a] Odds ratio adjusted for age. [b] 95% confidence interval.

Table 4. Use of oral contraceptives and other estrogens, and the relative risk of benign breast tumors

Factor	Benign tumor group			
	MCC (n = 56)	FAM (n = 25)	Cyst (n = 26)	Other (n = 49)
Use of oral contraceptive				
ever vs. never	2.1[a] (1.0, 4.3)[b]	1.0 (0.4, 2.8)	1.0 (0.4, 2.6)	1.3 (0.6, 2.8)
less than 5 years vs. never	1.7 (0.8, 3.8)	0.7 (0.2, 2.2)	1.2 (0.5, 3.3)	0.9 (0.3, 2.2)
5 years or more vs. never	3.2 (1.2, 8.4)	2.0 (0.6, 7.1)	0.4 (0.1, 3.3)	2.5 (0.9, 6.8)
Use of estrogen supplementation				
ever vs. never	1.4 (0.6, 3.3)	1.4 (0.3, 6.0)	NC[c]	0.5 (0.2, 1.3)
less than 4 years vs. never	1.2 (0.4, 3.7)	1.3 (0.3, 6.6)	NC	0.8 (0.2, 2.5)
4 years or more vs. never	1.5 (0.5, 4.7)	1.2 (0.1, 10.9)	NC	0.2 (0.1, 1.6)

MCC = mastopathia chronica cystica; FAM = fibroadenomatosis.
[a] Odds ratio adjusted for age. [b] 95% confidence interval. [c] No cases in one of the groups.

most studies not been related to the risk of any kind of BBD [12, 17–21].

Menopausal status has been associated positively with some types of BBD. The fact that premenopausal women seem to have an enhanced risk of both dysplasias and neoplasias [18, 22] is probably due to the effect of age discussed earlier.

Age at the time of first pregnancy and birth denotes the first true interruption to a woman's menstrual cycles and the related hormonal milieu. It is an established risk indicator for breast cancer, but its relation to various types of BBD is obscure. Many of the earlier studies found no statistically significant link between BBD and age at first birth [10–12, 19, 23]. Some demonstrated a slightly elevated risk of cystic disease with late age at first birth [17, 18, 20], but none reported a risk enhancement for fibroadenomas comparable to our results.

Our findings concur that continuous, uninterrupted menstrual activity from menarche to menopause, i.e. nulliparity, increases the general risk of BBD [10, 17, 21–23]. Other studies provide reasonably consistent results of greater parity providing protection against benign breast tumors [11, 17, 18, 23].

The only other study we know to have studied menstrual cycle length and BBD had results similar to ours: short cycles characterize increased risk [24]. Hislop and Elwood [25] also found regular menses as well as premenstrual breast tenderness to be associated with an increased risk. The latter authors have suggested that the systemic level of estrogen, rather than the duration of exposure to it, is more important as a determinant of BBD.

It is not surprising that mastitis appears to increase the probability of cyst formation, since inflammation is one of the clinical characteristics of duct ectasia [15]. The inflammatory environment of the infected glandular tissue can also cause hyperprolactinemia [26], which in turn could trigger mechanisms leading to the development of other types of BBD [27].

It has been suggested in the case of malignant breast tumors that the stature of a woman could be an important risk factor [28]. The theory suggests that the larger the total cell population the more susceptible cells there are to malignant transformation. The possibility has also been applied to benign breast tumors and with rather consistent results. Larger body size, denoted by greater height or BMI appears, however, to be protective rather than risk enhancing [10, 19, 21, 22]. Weight has been found to be more important than height as a determinant of BMI and risk [12, 20]. In our study population, breast size was not an independent protective factor but was related to BMI. At least in one study [25], BMI and large breasts have been found to be independent risk predictors, but it is difficult to reason the biological mechanisms for this phenomenon. The reason why heavy women with large breasts are protected against benign tumors may be related to a higher detection threshold rather than true lowering of risk. If this were true, the prevalence of these lesions should be independent of weight and BMI in autopsy series. Unfortunately, the published reports of this kind of study do not address this issue [29–31].

A number of earlier studies [6, 11, 14, 21, 22, 25, 32, 33] have found the use of oral contraceptives to increase rather than decrease the risk of chronic cystic disease. The number of OC users was quite low in our study and thus our findings could be due to small sample size. Another explanation is that offered by Janerich and coworkers [34] who noted that women with BBD were discouraged by their physician from continuing pill-use, thus creating a false impression of OC use preventing BBD. It is also of interest that LiVolsi and coworkers [35] found long-term use of OC's to protect against fibrocystic disease with minimal epithelial atypia, but not against disease with marked atypia.

In conclusion, we found that the risk profiles of various benign breast tumors appear to be rather different from each other. This highlights the need to keep the histological groups separate when evaluating the possible role of benign breast tumors in the etiology of breast cancer. It also emphasizes the need for an uniform histological classification system and nomenclature for benign breast tumors, such as suggested by Dupont and Page [36].

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